# Analgesic combination

The present invention relates to medicinal preparations which can be administered orally and contain a fixed combination of at least one locally acting analgesic with a rapid onset of action and at least one systemically acting analgesic with a sustained action.

Locally acting analgesics with a rapid onset of action which can be used, for example, in the form of sprays or pastilles are already known. Local anaesthetics of this type display their action after less than one minute but have only a short duration of action so that frequent remedication is necessary, which adversely affects safety and patient compliance.

Examples of particularly interesting locally acting analgesics which may be mentioned are the benzocaines. They inhibit impulse formation and conduction in nerves by blocking the flow of sodium.

Systemically acting analgesics, such as, for example, NSAIDs, in particular acetylsalicylic acid (ASA), represent another useful possibility for alleviating pain. These analgesics reduce the sensitivity of the nociceptors, and the alleviation of pain can be explained by the inhibition of prostaglandin synthesis. With most of these systemically acting analgesics, the maximum activity is not reached until after about 1-2 hours.

An object of the present invention is to satisfy the need, which has existed for a long time, to provide a preparation which can be administered orally and which combines, in a simple and reliable manner, an immediate analgesic action with a sustained action.

The active substances which can be used as locally acting analgesics (element A) are those which show a significant onset of action within a period of up to 10 minutes, preferably of 4 minutes, in particular of 1 minute and very particularly of 30 seconds.

The locally acting analgesics (combination element A) are expediently employed in amounts of from 0.5 to 100 mg, preferably 1 to 60 mg and, in particular, 2 to 30 mg, per individual administration form.

The combination according to the invention may contain one or more local anaesthetics as element A, for example 1, 2 or 3. Combinations with only one compound of element A are of particular interest.

The active substances of element A are substantially known. Particularly suitable examples which may be mentioned are ester-type local anaesthetics such as benzocaine, amethocaine, amylocaine, butacaine, butoxycaine, butyl aminobenzoate, chloroprocaine, chlormecaine, cyclomethycaine, isobutamben, meprylcaine, oxybuprocaine, procaine, propipocaine, proxymetacaine, tricaine etc. Mention may likewise be made of anilide-type local anaesthetics such as lidocaine, bupivacaine, butanilicaine, carticaine, cinchocaine, clibucaine, etidocaine, mepivacaine, oxethazaine, prilocaine, ropivacaine, ethyl p-piperidinoacetyl-aminobenzoate, tolycaine, trimecaine, vadocaine, etc.

It is also possible to employ other local anaesthetics such as, for example, pramoxine or essential oils such as menthol or eucalyptus oil.

The systemically acting analgesics which can be employed as element B are likewise substantially known. Mention may preferably be made of non-steroidal antiinflammatory drugs (NSAIDs) such as, for example, phenylacetic acid derivatives such as aceclofenac, alclofenac, bromofenac, diclofenac, fenclofenac etc., arylacetic acid derivatives such as acemetacin, amfenac sodium, bendazac, glucametacin, oxametacin, etc., para-aminophenol derivatives such as acetanilide, etc., propionic acid derivatives such as alminoprofen, ibuprofen, ketoprofen, flurbiprofen, naproxen, oxaprozin, salicylic acid derivatives such as acetylsalicylic acid (ASA), aluminium ASA and other salts, diflunisal, etersalate, fosfosal, salol, salsalate, salacetamide, etc., pyrazolone derivatives such as amidopyrine, dipyrone etc., oxycam derivatives such as droxicam, isoxicam, piroxicam etc., phenylbutazone derivatives such as azapropazone, bumadizone calcium, oxyphenbutazone etc., pyranoindoleacetic acid derivatives such as etodolac etc., anthranilic acid derivatives such as glafenine, Na meclofenamate, mefenamic acid, morniflumate etc., indole derivatives such as indomethacin etc., paracetamol and paracetamol derivatives and other NSAIDs such as anirolac, benzpiperylone, benzydamine hydrochloride, Na butibufen, chlorthenoxazine, cinmetacin, clonixin, cloracetadol, difenpiramide, diproqualone, etenzamide, famprofazone, flupirtine maleate, ibuproxam, indoprofen, isamfazone, meloxicam, metiazinic acid, metifenazone, nifenazone, niflumic acid, mimesulide, pirazolac, pranoprofen, proquazone, protizinic acid, ramifenazone etc.

The systemically acting analgesics of element B are employed according to the invention in amounts of from 5 to 1500 mg, preferably 8 to 1000 mg, in particular 10 to 800 mg, per dosage form.

The local analgesics preferably employed as element A are rapidly acting and have an optimal duration of action lasting 0.5 to 120 minutes, preferably 2 to 60 minutes, in particular 5 to 30 minutes. The systemic analgesics preferably used as element B are those where a significant action has its onset after 15 minutes and lasts for up to 24 hours, preferably those whose action has its onset after 20 minutes and lasts for up to 12 hours, in particular up to 8 hours.

Particularly interesting combinations according to the invention are those which contain as element A an ester-type local anaesthetic, in particular benzocaine, and contain as element B propionic acid derivatives or salicylic acid derivatives, in particular ASA.

Preferred systemic analgesics are those which have a duration of action of at least 3 hours.

The combination according to the invention is particularly suitable for treating inflammatory and/or painful disorders of the oropharynx, in particular for treating pharyngitis, laryngitis, tonsillitis, stomatitis, gingivitis of a variety of aetiologies. The combination product according to the invention is expediently administered orally.

The combination can be employed in conventional formulations, the intention being that the local anaesthetic is released first, and it being possible for the systemically acting analgesic where appropriate also to be present in depot form. The following may be mentioned as examples of such preparations: press-coated tablets, coated pastilles, chewing gum, hard caramel with liquid, semisolid or solid core. They are produced by conventional methods using customary ancillary substances.

## Examples

### Example 1

A tablet of the following composition may be mentioned by way of example:

ASA core tablet:

500 mg of ASA are compressed with 30 mg of ascorbic acid, 75 mg of sucrose, 47 mg of microcrystalline cellulose, 2 mg of saccharin (550 ×) and 6 ml of orange juice flavouring to give a tablet with a total weight of 660 mg. These core tablets are coated uniformly with a benzocaine-containing coating syrup, applying a total of about 5 mg of benzocaine and 602 mg of coating syrup. The aforementioned tablet shows a marked analgesic action only two minutes after intake, and this is sustained for a period of more than 3 hours.

### Example 2

A core tablet containing 300 mg of naproxen is coated with a coating syrup which contains 500 mg of lidocaine in analogy to Example 1. This combination preparation shows an onset of action after 2 minutes and a duration of action of more than 6 hours.